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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/121,587	07/23/1998	THOMAS J. CHAMBERS	06132/033003	3485

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EXAMINER

ZEMAN, ROBERT A

ART UNIT PAPER NUMBER

1645

DATE MAILED: 03/21/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/121,587

Applicant(s)

CHAMBERS ET AL.

Examiner

Robert A. Zeman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 January 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-29 is/are pending in the application.
- 4a) Of the above claim(s) 3-5, 11-13 and 17-29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 6-10 and 14-16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1-29 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

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DETAILED ACTION

The amendment filed on 1-6-2003 is acknowledged. Claims 9-10 have been amended. This application contains claims 3-5, 11-13, and 17-29 drawn to an invention nonelected with traverse in Paper No. 18. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Specification

The substitute specification filed on 1-6-2003 is acknowledged and has been entered.

Objections Withdrawn

The objection to the specification for the improper use of trademarks is withdrawn in light of the entry of the substitute specification.

Claim Rejections Maintained

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

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The provisional rejection of claims 1, 2, 6-10 and 14-16 under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 2, 6-7, 9-11 and 15-18 of copending Application No. 09/452638 is maintained for reasons of record. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Applicant argues:

1. The rejection should be withdrawn in accordance with M.P.E.P. 822.01.

Applicant's arguments have been fully considered and deemed non-persuasive. Since the aforementioned rejection is not the sole remaining rejection M.P.E.P. 822.01 does not apply.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 9-10 and 14-16 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for therapeutic/prophylactic use of the chimeric virus YF/JE SA₁₄₋₁₄₋₂ RMS or YF/JE_{Nakayama} against Japanese encephalitis virus infection, does not reasonably provide enablement for the therapeutic/prophylactic use of **any other** chimeric flavivirus, nor does it provide enablement for the therapeutic/prophylactic use of the chimeric virus YF/JE SA₁₄₋₁₄₋₂ RMS or YF/JE_{Nakayama} against anything other than Japanese encephalitis virus infection is maintained for reasons of record.

Applicant argues:

1. The specification discloses the efficacy of the YF/JE Nakayama chimera.

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2. The paper by Guirakhoo et al. (Virology 74(12):5477-5485, 2000) discloses the efficacy of an YF/Dengue 2 chimera.

3. The paper by Arroyo et al. (Trends Mol. Med. 7:2350-2354, 2001) discloses the efficacy of an YF/West Nile 2 chimera.

Applicant's arguments have been fully considered and deemed non-persuasive.

Applicant's assertion that the specification demonstrated the efficacy of the YF/JE Nakayama chimera is well founded. Consequently, the aforementioned rejection has been modified. However, contrary to Applicant's assertion, the post filing references by Guirakhoo et al. and Arroyo et al. do not demonstrate that the specification would enable any person skilled in the art to which it pertains, or with which it is most nearly connected (at the time of the invention), to use the invention commensurate in scope with these claims. Said reference does disclose two chimeras that have efficacy as a prophylactic. However, based on the instant specification, one of skill in the art would not have been able to predict that said chimeras (or any other chimera) would be effective prophylactics. As noted previously, the instant specification fails to provide direction (i.e. which sequences must be added to the YF backbone etc.) on which chimeric viruses, other than SA₁₄-14-2 RMS or YF/JE_{Nakayama} would elicit a therapeutic or prophylactic response. Moreover, it appears that the primers utilized by Guirakhoo et al. differ from the ones disclosed in the instant application for the generation of an YF/DEN-2 chimera (see page 63 of the specification and page 5478 of Guirakhoo et al.). Consequently, given the lack of success in the art, the lack of working examples and the unpredictability of the generation of a therapeutic or prophylactic response in a living organism, the specification is not enabling for the therapeutic/prophylactic use of chimeric flavivirus other than SA₁₄-14-2 RMS or

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YF/JE_{Nakayama}, nor does it provide enablement for the therapeutic/prophylactic use of the chimeric virus YF/JE SA₁₄-14-2 RMS or YF/JE_{Nakayama} against anything other than Japanese encephalitis virus infection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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The instant claims are drawn to a chimeric, live, infectious virus comprising a yellow fever virus (first virus) in which the nucleotide sequence encoding the prM-E protein is modified such that the functional YF virus prM-E protein is not expressed, and integrated into said YF virus a nucleotide sequence encoding a prM-E protein of a second, different flavivirus, specifically the Japanese Encephalitis virus, so that the prM-E of said second virus is expressed. The claims are further drawn to the chimeric virus wherein the nucleotide sequence encoding the prM-E protein of the second flavivirus comprises a mutation that prevents prM cleavage to produce M protein while maintaining the NS2-B-3 protease recognition site and signal sequences and cleavage sites at the C/prM and E/NS1 junctions.

The rejection of claims 1-2, 6-10 and 14-16 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Lai et al. (WO 93/06214—IDS-22) is maintained for reasons of record.

Applicant argues:

1. The focus of Lai et al. is chimeras that include structural proteins from tick-borne encephalitis virus and non-structural proteins of dengue virus, as well as intertypic dengue chimeras.
2. In most of the chimeras described in the Lai publication, all 3 structural proteins (C, prM and E) of one flavivirus is replaced with those of another.
3. Lai et al. disclose only two specific examples of chimeras including non-structural and capsid proteins from the first virus and pre-membrane and envelope proteins from another virus. Said examples utilize a dengue virus as the first virus and either TBEV or Japanese encephalitis virus as the second virus.

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4. Lai et al. disclose on page 21 lines, 24-33 that said chimeras are unexpected and do not suggest that such chimeras be made using other flaviviruses such as yellow fever virus as the source of the non-structural and capsid proteins.
5. The only context in which yellow fever virus is mentioned by Lai et al. is in a chimera in which the sources of all structural and all non-structural proteins are different.
6. Lai et al. do not describe a yellow fever based chimera that includes the non-structural and capsid proteins of the yellow fever virus and the pre-membrane and envelope proteins of another flavivirus as is required by the instant claims.
7. The dengue-based chimera described by Lai et al. have the TBEV signal sequence that lies between the prM and C in addition to the TBEV prM and E proteins.
8. This approach when used with a Yellow virus backbone (first virus) and dengue as the source of the structural sequence does not produce a viable chimera. Hence, the prior art teaches away from the approach of the instant invention.

Applicant's arguments have been fully considered and deemed non-persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the capsid protein must be from the first virus (i.e. yellow fever virus) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

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As outlined previously, Lai et al. disclose an attenuated chimeric flavivirus particle comprising a region of nucleotide sequences encoding the non-structural proteins (NS) of the yellow fever virus and a region of nucleotide sequences encoding the structural protein prM-E of a flavivirus selected from a dengue virus (serotype 1, 2, 3 and 4), Japanese encephalitis virus, tick-borne encephalitis virus (specifically) and a flavivirus (generally). Lai et al. specifically disclose the DNA fragment that encodes a dengue virus protein comprising mutations at the C-terminal of the NS1 gene, resulting in the prevention of the NS1 protein cleavage (see examples 8-12). Lai et al. further disclose the use of said chimeric flaviviruses as a vaccine (see example 21) and methods of producing said chimeric viruses recombinantly (see example 17). While Lai et al. do not explicitly disclose methodologies (i.e. provide working examples) using the Yellow Fever virus and the Japanese encephalitis virus such a chimeric was contemplated (see claim 38). Moreover, Lai et al. disclose 'a chimeric virus for use in vaccine preparation having a genome comprising nucleic acid sequences encoding at least one structural protein from one flavivirus and nucleic acid sequences encoding nonstructural proteins from another (see abstract and page 6, lines 18-25). Therefore, while not explicitly disclosed in the working examples, the Yellow Fever/Japanese encephalitis combination would be an obvious variant of the chimerics disclosed by Lai et al.

The rejection of claims 1-2, 6-10 and 14-16 under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Lai et al. (U. S. Patent 6,184,024—IDS-29) is maintained for reasons of record.

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Applicant argues:

1. In most of the chimeras described in the Lai publication, all 3 structural proteins (C, prM and E) of one flavivirus ^{are} replaced with those of another.
2. Lai et al. disclose only two specific examples of chimeras including non-structural and capsid proteins from the first virus and pre-membrane and envelope proteins from another virus. Said examples utilize a dengue virus as the first virus and either TBEV or Japanese encephalitis virus as the second virus.
3. The only context in which yellow fever virus is mentioned by Lai et al. is in a chimera in which the sources of all structural and all non-structural proteins are different.
4. Lai et al. ~~do~~ not describe a yellow fever based chimera that includes the non structural and capsid proteins of the yellow fever virus and the pre-membrane and envelope proteins of another flavivirus as is required by the instant claims.

Applicant's arguments have been fully considered and deemed non-persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the capsid protein must be from the first virus)(i.e. yellow fever virus) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

As outlined previously, Lai et al. disclose an attenuated chimeric flavivirus particle comprising a region of nucleotide sequences encoding the non-structural proteins (NS) of the

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yellow fever virus and a region of nucleotide sequences encoding the structural protein prM-E of a flavivirus selected from a dengue virus (serotype 1, 2, 3 and 4), Japanese encephalitis virus, tick-borne encephalitis virus (specifically) and a flavivirus (generally). Lai et al. specifically disclose the DNA fragment that encodes a dengue virus protein comprising mutations at the C-terminal of the NS1 gene, resulting in the prevention of the NS1 protein cleavage or 3' mutations resulting in reduced glycosylation of prM, E or NS1 resulting in reduced cleavage of the prM protein (see examples 9-16). Lai et al. further disclose the use of said chimeric flaviviruses as a vaccine (see example 23-24) and methods of producing said chimeric viruses recombinantly (see example 22). While Lai et al. do not explicitly disclose methodologies (i.e. provide working examples) using the Yellow Fever virus and the Japanese encephalitis virus such a chimeric was contemplated (see claims 1 and 8). Moreover, Lai et al. disclose 'a chimeric virus for use in vaccine preparation having a genome comprising nucleic acid sequences encoding at least one structural protein from one flavivirus and nucleic acid sequences encoding nonstructural proteins from another (see abstract and column 5, lines 58-67). Therefore, while not explicitly disclosed in the working examples, the Yellow Fever/Japanese encephalitis combination would be an obvious variant of the chimerics disclosed by Lai et al.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO**

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MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Robert A. Zeman
March 17, 2003